REMARKS

Summary of Interview

On August 5, 2002, inventor Dr. Judith Varner, Applicant's representative Dr. Maha Hamdan, Examiner Susan Ungar, and Supervisory Examiner Anthony Caputa conducted an interview in which the rejections in the Final Office Action mailed on May 21, 2002 were discussed.

In particular, with respect to the rejections based on alleged indefiniteness and inadequate written description,[1] the Examiner requested further clarification of case law relating to the consideration of declarations. This is provided in items 1-3 of this communication.

Regarding the rejection based on alleged non-enablement,[2] the Examiner requested further highlighting Applicant's arguments that Ruoslahti *et al.* does not support non-enablement. This is provided in item 4 of this communication.

Referring to the rejection based on alleged anticipation[3] and obviousness,[4] Dr. Varner explained at the interview that Pasqualini *et al.*'s superfibronectin is **not an α5β1 antagonist**. This is supported by, for example, the **newly submitted evidence**[5] which demonstrates that upregulated fibronectin expression *in vivo* is associated with angiogenesis rather than with reduced angiogenesis. In this regard, the Examiner's attention is respectfully drawn to amended Claims 1, 55, and 57 (and new Claims 121-123) which recite an "α5β1 antagonist," and to Applicant's additional evidence and arguments in items 5-9 of this communication.

The Examiner requested amendment of the claims to recite an additional distinction between the recited "agent" and Pasqualini *et al.*'s superfibronectin which reflects that superfibronectin is not an α5β1 antagonist. In this regard, the Examiner's attention is drawn to new Claims 121-123 which recite that the α5β1 antagonist "induces endothelial cell

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[1] Office Action, items 4-6, pages 2-4.

[2] Office Action, item 7, pages 4-7.

[3] Office Action, item 8-10, pages 7-12.

[4] Office Action, items 11-12, pages 12-17.

[5] Clark *et al.* (1982) (Tab 1); Castellani *et al.* (1994) (Tab 2); Neri *et al.* (1997) (Tab 3); and Mariani *et al.* (1997) (Tab 4).

apoptosis."[6] The Examiner's attention is also drawn to Applicant's additional evidence and arguments in items 5-9 of this communication.

Status of the Application

Claims 1-5, 9-14, 19, 20, 55-72, 75, and 80-120 are pending in the present application. Following entry of this amendment, Claims 1-5, 9-14, 19, 20, 55-72, 75, and 80-123 will be pending.

The claims have been amended to better define particular embodiments of the invention, notwithstanding Applicant's belief that the unamended claims would have been allowable, without acquiescing to any of the Examiner's arguments, and without waiving the right to prosecute the unamended (or similar) claims in another application, but rather for the purpose of furthering Applicant's business goals and expediting the patent application process in a manner consistent with the PTO's Patent Business Goals (PBG).[7]

In particular, Claims 1, 55, and 57 have been amended by replacing the term "agent" with "α5β1 antagonist." Support for this amendment is found in the Specification at, for example, page 5, lines 8-12, page 14, lines 2-4, page 18, lines 12-20, page 19, lines 24-27 which teach that the terms "agent" and "α5β1 antagonist" are equivalent. This is not a narrowing amendment since it para-phrases the originally-filed recitation, rather than narrows it.

Dependent Claims 2, 13, 19, 65-67, 70-72, 75, 80, 82, 84, 86, 90, 92, 94, 96, 106, 108, 110, 112, 114, 116, 117, and 119 have been amended to provide antecedent basis.

New Claims 121-123 recite that the α5β1 antagonist "induces endothelial cell apoptosis" as supported by the Specification, page 16, lines 25-28, which teaches that "α5β1 antagonists also induce apoptosis of growth factor stimulated endothelial cells *in vitro* and *in vivo*." This is not a narrowing amendment because it describes a property of the α5β1 antagonists, rather than narrows the scope of the claims.

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[6] Applicant avers that this amendment is not made in acquiescence to the Examiner's contention that further distinction of an "agent" over superfibronectin is necessary to impart novelty or non-obviousness. Rather, this amendment is made to expedite Applicant's business interests.

[7] 65 Fed. Reg. 54603 (September 8, 2000).

The Examiner maintained the following rejections of the claims:

1. Claim 2 continues to be rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness;

2. Claims 80-86, 90-96, and 110-116 remain rejected under 35 U.S.C. §112, first paragraph, for alleged lack of adequate written description;

3. Claims 86, 96, and 116 continue to be rejected under 35 U.S.C. §112, first paragraph, for alleged lack of adequate written description;

4. Claims 80-120 remain rejected under 35 U.S.C. §112, first paragraph, for alleged non-enablement;

5. Claims 1-5, 9-13, 55-66, 68, 69, 71, 72, 75, and 80-120 continue to be rejected under 35 U.S.C. §102(e) as being allegedly anticipated by Pasqualini *et al.* (U.S. Patent No. 5,922,676);

6. Claims 1-3, 9-13, 55, 57-63, 65, 66, 71, 72, 75, 80-97, 100-106, 108-117, 119, and 120 remain rejected under 35 U.S.C. §102(e) as being allegedly anticipated by Pasqualini *et al.* (U.S. Patent No. 5,922,676) as evidenced by Ruoslahti *et al.* (WO 95/14714);

7. Claims 80-106, 108-117, 119, and 120 continue to be rejected under 35 U.S.C. §102(e) for alleged anticipation by Pasqualini *et al.* (U.S. Patent No. 5,922,676) as evidenced by Ruoslahti *et al.* (WO 95/14714) and Pytela *et al.*;

8. Claims 1-5, 9-13, 19, 20, 55-72, 75, 80-106, 108-117, 119, and 120 remain rejected under 35 U.S.C. §103(a) for alleged obviousness over Pasqualini *et al.* (U.S. Patent No. 5,922,676) as evidenced by Ruoslahti *et al.* (WO 95/14714), Thorpe, and Pytela *et al.*; and

9. Claims 1-5, 9-14, 19, 20, 55-72, 75, and 80-120 stand rejected under 35 U.S.C. §103(a) for alleged obviousness over Pasqualini *et al.* (U.S. Patent No. 5,922,676) as evidenced by Ruoslahti *et al.* (WO 95/14714).

Applicant believes that the following remarks traverse the Examiner's rejection of the claims. These remarks are presented in the same order as they appear above.

1. **Rejection Of Claim 2 Under 35 U.S.C. §112, Second Paragraph**

Claim 2 continues to be rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness of the term "substantially."[8] Applicant respectfully must disagree, and incorporates herein each of her prior arguments and evidence that were presented in the Responses mailed on 2/19/02 and 9/5/01, including a Declaration of Dr. Virgil L. Woods Jr. Applicant was surprised that Dr. Woods' Declaration was not considered and that the rejection remains.

The Examiner maintained the rejection in the face of Dr. Woods' Declaration on the ground that "If Dr. Woods understands the scope of the claims after discussion with Applicant, this understanding does not provide clarification for *the public, at large*, for the reasons previously set forth."[9]

However, as discussed at the interview, the Examiner's ground is improper for the following reasons. First, the Examiner improperly formulated her conclusion without **any regard** to Dr. Woods' Declaration, much less **an explanation** of the Declaration's deficiency. The Federal Circuit in *Alton* has held that:

> "The examiner . . . erred by dismissing the . . . declaration without an adequate explanation of how the declaration failed to overcome the . . . rejection."[10]

In *Alton*, the examiner summarily dismissed a declaration providing factual support for a conclusion that a claimed composition of matter was adequately described in the specification. The Court found this dismissal **erroneous**, and stressed that the declaration contained factual statements to support its conclusion and that it is the burden of the examiner to address each of these factual statements and explain why they are incorrect or unpersuasive.

In the instant case, the Examiner admitted that she arrived at her conclusion **before** receiving a copy of Dr. Woods' Declaration; the Examiner stated that "no Declaration was received with this response."[11] Applicant forwarded another copy of Dr. Woods' Declaration

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[8] Office Action, page 2, item 4.

[9] (Emphasis added) Office Action, page 3, second paragraph.

[10] *In re Alton,* 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

[11] Office Action, page 3, second paragraph.

to the Examiner via facsimile on July 1, 2002, **after** the instant Office Action was mailed. Since Dr. Woods' Declaration was summarily disregarded, it stands unrebutted.

Second, the Examiner is respectfully reminded that the test of definiteness relates to the understanding of those skilled in the art, **not** of the public at large.

> "A decision as to whether a claim is invalid under [§112 ¶2] requires a determination whether those skilled in the art would understand what is claimed."[12]

Since the Examiner places a greater burden than that required by the law, her ground for the rejection cannot rebut Dr. Wood's Declaration who **is** qualified to speak on the level of ordinary skill in the fields of integrin biology and biochemistry.[13] Dr. Woods indicated that he understand the meaning of the term "substantially" in Claim 2, and specifically referred to the mathematical ranges recited in the Specification. Since one of skill (Dr. Woods) comprehends the term "substantially," the rejection should be withdrawn.

Third, the Examiner has not provided **any technical evidence** to rebut Dr. Woods' Declaration but instead relied on assertions. The Federal Circuit has held that where the patentee submitted a declaration which explains why one of skill in the art studying the specification would have understood the recited limitation, the statutory rejection cannot stand where the patent challenger

> "submitted no *technical evidence* to refute [the declarant's] conclusions."[14]

Because the Examiner's rebuttal falls short of the legal requirement, Dr. Woods' Declaration stands unrebutted.

Fourth, the Examiner is respectfully reminded that claim terms are definite even if disagreement exists (which has not been established) with respect to the meaning of the terms. The Federal Circuit has held that:

> "If the meaning of a claim is discernible, even though the task may be formidable and the conclusion may be one over which

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[12] *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1217 , 18 USPQ2d 1016 (Fed. Cir. 1991).

[13] Declaration by Dr. Woods, item 1.

[14] (Emphasis added) *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1116 (Fed. Cir. 1991).

> reasonable persons will disagree, we have held the claim sufficiently clear to avoid invalidity on indefiniteness grounds."[15]

Thus, even if the Examiner (who is not "one skilled in the art")[16] disagrees with Dr. Woods' conclusion, this does not negate definiteness because the courts have found the term "substantial" to be definite even in the face of disagreement.[17]

In view of the above, Applicant respectfully requests withdrawal of the rejection of Claim 2 under 35 U.S.C. §112, second paragraph.

2. Rejection Of Claims 80-86, 90-96, And 110-116 Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 80-86, 90-96, and 110-116 stand rejected under 35 U.S.C. §112, first paragraph, for alleged lack of adequate written description.[18] Applicant respectfully disagrees, and incorporates herein each of her prior arguments and evidence that were presented in the Responses mailed on 2/19/02 and 9/5/01.

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[15] *Exxon Research and Engineering Co. v. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001).

[16] *Stratoflex, Inc. v. Aroquip Corp.*, 218 USPQ 871, 879 (Fed. Cir. 1983).

[17] *Amtel Corp. v. Information Storage Devices, Inc.*, 997 F.Supp. 1210, 1228 (N.D.Cal. 1998) held term "substantially all" to be definite; *Pave Tech, Inc. v. Snap Edge Corp.*, 952 F.Supp. 1284, 1292 (N.D.Ill. 1997) held term "substantially" when considered in light of entire claimed invention, was as accurate as subject matter permitted, and provided sufficient guidance to one skilled in the art; *James River Corp. of Virginia v. Hallmark Cards*, 915 F.Supp. 968, 989 (E.D.Wisc. 1996) held word "substantially" in term "substantially integrated" was sufficiently defined, since one skilled in the art would recognize the difference between prior art and the claimed invention; *BOC Health Care, Inc. v. Nellcor Corp.*, 892 F.Supp. 598, 613 (D.Del. 1995) found phrase "substantially planar" to be sufficiently defined to those skilled in the art; *York Products, Inc. v. Central Tractor Farm & Family Center*, 99 F.3d 1568 (Fed. Cir. 1996) held "substantial" did not render a claim indefinite. The court accorded the word "substantially" its normal meaning, stating: "ordinarily, therefore, 'substantially' means considerable in . . . extent, . . . , or 'largely but not wholly that with is specified." 99 F.3d at 1572-73.

[18] Office Action, page 3, item 5.

The Examiner maintained her contention that support is lacking for "the limitation of an agent wherein binding of said agent to alpha 5 beta 1 integrin is at least two-fold, five-fold, ten fold greater than the binding of said agent to an integrin other than alpha 5 beta 1" because "the support is drawn only to *peptides* and not to the broadly claimed '*agent.*'"[19]

As discussed at the interview, this contention is legally unsound for two reasons. First, the Examiner **did not even consider** Dr. Woods' Declaration (which she did not receive until **after** the instant Office Action was mailed) let alone provide **an explanation** of the Declaration's deficiency. The Examiner is respectfully reminded that:

> "any affidavits relevant to the 35 U.S.C. 112, para. 1, written description requirement *must be thoroughly analyzed and discussed* in the next Office action."[20]

In fact, the Examiner stated that "no Declaration was received with this response thus, it is not possible to either consider or evaluate the Declaration."[21] Because the Examiner improperly disregarded the content of the Declaration, the Declaration's import is unrebutted.

Second, **no technical evidence** was advanced by the Examiner to rebut Dr. Woods' Declaration. This is similar to the facts in *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1116 (Fed. Cir. 1991) where the Federal Circuit **reversed** a summary judgment of lack of adequate written description where the patentee submitted a declaration which "explains why one of skill in the art . . . studying the drawings . . . would have understood from them [the recited limitation]" and where the patent challenger "submitted no technical evidence to refute [the declarant's] conclusions." Since technical evidence which counters Dr. Woods' Declaration is absent, the Declaration stands unrebutted.

In commenting on the Declaration, the Examiner stated that "even were the Declaration, as described, to be submitted and considered *it is not relevant whether or not the inventor was in possession at the time the invention was made* since it appears that the

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[19] (Emphasis added) Prior Office Action, Paper 15, page 16, item 10.

[20] (Emphasis added) MPEP 2163.05, citing *In re Alton,* 76 F.3d 1168, 1176, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996) ("The examiner . . . erred by dismissing the . . . declaration without an adequate explanation of how the declaration failed to overcome the . . . rejection.")

[21] Office Action, page 4, first paragraph.

inventor chose not to mention this broadly claimed limitation in the specification or claims as originally filed."[22]

As discussed at the interview, this comment reflects a misunderstanding of the law of "written description." The written description requirement is satisfied if the disclosure by Applicant

> "convey[s] with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she *was in possession of the invention*."[23]

Thus, contrary to the Examiner's assertion that "it is not relevant," the inventor's possession of the claimed invention at the time of filing is fundamental to the written description inquiry. Dr. Woods, who is skilled in the art[24] addressed this fundamental inquiry by referring to the Specification's teachings at page 18, lines 7-15, page 19, lines 24-27, and page 23, lines 5-14[25] and by concluding therefrom that written description **is** satisfied.[26]

In view of Dr. Woods's Declaration, withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

3. Rejection Of Claims 86, 96, And 116 Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 86, 96, and 116 stand rejected under 35 U.S.C. §112, first paragraph, for alleged lack of adequate written description for "an agent which does not interfere with the *specific binding* of a ligand to any integrin since the support is only drawn to *fold-affinity*."[27] Applicant respectfully disagrees, and incorporates herein each of her prior arguments and evidence that were presented in the Responses mailed on 2/19/02 and 9/5/01, and reiterates

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[22] (Emphasis added) Office Action, page 4, first paragraph.

[23] (Emphasis added) *In re Alton,* 37 USPQ2d 1578 (Fed. Cir. 1996), citing *Vas-Cath, Inc. v. Mahurkar,* 935 F.2d 1555; 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).

[24] Declaration by Dr. Woods, item 1.

[25] Declaration by Dr. Woods, items 6 and 7.

[26] Declaration by Dr. Woods, item 7.

[27] (Emphasis added) Prior Office Action, Paper No. 15, page 17, first paragraph.; instant Office Action, page 4, item 6.

her above arguments (item 2). Accordingly, it is respectfully requested that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

4. Rejection Of Claims 80-120 Under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 80-120 stand rejected under 35 U.S.C. §112, first paragraph, for alleged non-enablement.[28] Applicant respectfully must traverse.

Applicant highlights the following arguments that relate to Ruoslahti *et al.*'s disclosure and that were discussed with the Examiner at the interview on August 5, 2002. Ruoslahti *et al.* discloses using peptides to inhibit metastasis of tumor cell lines, and to inhibit cell attachment of these cell lines to fibronectin.[29] Ruoslahti *et al.* used the following tumor cell lines: B2/α27 cells, C8161 cells, MG-63 cells, and WI-38 cells, "which all express α5β1."[30] The Examiner alleged non-enablement of agents which bind to α5β1 integrin with **less than** 100-fold greater affinity to α5β1 than to another integrin. This allegation is unsound for three reasons.

First, at best, this ground of rejection can arguably be directed at only Claims 80-85, 90-95, 110,-115 which recites the relative fold binding of the agent to α5β1 as compared to another ligand.

Second, Ruoslahti *et al.*'s data is irrelevant to non-enablement of the instantly claimed invention because their data relates to the effect of peptides on **epithelial** tumor cells, not **endothelial** cells. In particular, Ruoslahti *et al.* used **epithelial** tumor **cell lines** which are devoid of endothelial cells that are engaged in the recited "angiogenesis." Nothing in Ruoslahti *et al.* or the prior art teaches that the effect of peptides on Ruoslahti *et al.*'s epithelial cells may be extrapolated to endothelial cells.

Third, even if Ruoslahti *et al.*'s data were erroneously extrapolated to the endothelial cells of the instantly claimed invention, it is notable that Ruoslahti et al. **nowhere** teaches or

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[28] Office Action, page 4, item 7.

[29] Ruoslahti *et al.*, Figures 5 and 11; page 5, lines 24-25; page 6, fifth paragraph; page 31, lines 11-34; and page 32, lines 1-8.

[30] Ruoslahti *et al.*, paragraph bridging pages 31 and 32.

suggests that a peptide binding affinity to α5β1 integrin that is **less than** 100-fold greater than to another integrin is inoperable. Said differently, Ruoslahti *et al.* does **not** teach that peptides with a 2-99, 5-99, and 10-99 fold greater affinity to α5β1 integrin compared to another integrin **fail** to reduce metastasis or cell migration of epithelial cells (even if epithelial cell data were arguably representative of endothelial cell data, which it is not).

Furthermore, Applicant incorporates herein each of her prior arguments and evidence that were presented in the Responses mailed on 2/19/02 and 9/5/01. In particular, Applicant argued that (1) **enablement is admitted** by the Examiner because each of the rejected Claims 80-120 depends directly or indirectly from the admittedly enabled Claims 1, 10, 12, 55, and 57, (2) the art's definition of the term "selective binding" is **irrelevant** because this term is not recited in (albeit it is encompassed by) any of the rejected claims, (3) the law does **not** require numerical limits for clarity of "specific binding," (4) the **numerical** values which Ruoslahti *et al.* use to define their use of the term "specific binding" are irrelevant to the instant invention's **qualitative** definition of the term "specific binding," (5) the Specification and prior art teach exemplary **routine** methods to determine the recited "reducing or inhibiting angiogenesis," (6) the Specification teaches using an exemplary **routine** α5β1 integrin receptor ligand binding assay to determine the recited interference "with specific binding of the α5β1 integrin to a ligand," (7) the Specification teaches using an exemplary **routine** integrin receptor ligand binding to quantitatively determine whether the level of association of the agent to α5β1 is the recited at least two-fold, five-fold, or ten-fold greater than that to another ligand, (8) even if (for the sake of argument) agents with less than 100-fold greater affinity to α5β1 than to another integrin did not result in the recited reduction of angiogenesis, the inclusion of inoperative embodiments does **not** negate enablement, and (9) "successful therapy" is **irrelevant** because it is not recited in (albeit it is encompassed by) the rejected claims.

In view of the above, Applicant respectfully requests that the rejection under 35 U.S.C. §112, first paragraph, for alleged non-enablement be withdrawn.

5. Rejection Of Claims 1-5, 9-13, 55-66, 68, 69, 71, 72, 75, And 80-120 Under 35 U.S.C. §102(e) Over Pasqualini *et al.*

Claims 1-5, 9-13, 55-66, 68, 69, 71, 72, 75, and 80-120 stand rejected under 35 U.S.C. §102(e) as being allegedly anticipated by Pasqualini *et al.* (U.S. Patent No. 5,922,676).[31] Applicant respectfully traverses since Pasqualini *et al.* does not disclose each and every element of the claimed invention.

As discussed at the interview, Pasqualini *et al.* does not disclose that its sFN is an "α5β1 antagonist."[32] To the contrary, sFN functions as an **α5β1 ligand** rather than an **α5β1 antagonist**. For example, Applicant's previously submitted evidence shows that whereas sFN **promotes** cell adhesion through α5β1 integrin and other receptors,[33] α5β1 antagonists do **not promote** cell adhesion (Tab 6).[34]

Importantly also, to the extent that the Examiner equates sFN and fibronectin, Applicant's **newly submitted evidence** demonstrates that upregulated fibronectin expression is associated with *in vivo* **angiogenesis** rather than with **reduced angiogenesis**. In particular, Clark *et al.* (1982)[35] (Tab 1) shows that fibronectin is expressed in large amounts surrounding new capillaries in healing skin wounds and that its expression subsides once angiogenesis is complete. Castellani *et al.* (1994)[36] (Tab 2) shows that an alternatively spliced form of

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[31] Office Action, page 7, item 8.

[32] This amendment is not made in acquiescence to the Examiner's contention that further distinction of an "agent" over superfibronectin is necessary to impart novelty or non-obviousness. Rather, this amendment is made to expedite Applicant's business interests.

[33] Morla *et al.*, pages 195, 196, and Figure 4.

[34] Kumar *et al.* (1997) "Biochemical characterization of the binding of echistatin to integrin αvβ3 receptor," Journal of Pharmacology and Experimental Therapeutics, 283(2):843-853; Attached at Tab 6; See pages 850 and 852. See also Varner *et al.* (1995).

[35] Clark *et al.* "Blood vessel fibronectin increases in conjunction with endothelial cell proliferation and capillary ingrowth during wound healing." J Invest Dermatol. 1982 Nov;79(5):269-76.

[36] Castellani *et al.* "The fibronectin isoform containing the ED-B oncofetal domain: a marker of angiogenesis." Int J Cancer. 1994 Int.J.Cancer 59:612-618.

fibronectin, ED-B, which retains integrin α5β1 binding sites, but which expresses an epitope that is unique from plasma fibronectin, is found in association with new blood vessels but not mature ones. Neri *et al.* (1997)[37] (Tab 3) shows that antibodies targeted to oncofetal fibronectin (ED-B) detect angiogenic, but not resting, blood vessels in tissues. Last, but not least, Mariani *et al.* (1997) (Tab 4)[38] shows that an antibody to oncofetal fibronectin detects tumors *in vivo* in mice.

In addition, Applicant incorporates herein each of her prior arguments and evidence that were presented in the Responses mailed on 2/19/02 and 9/5/01 in support of her position that express and inherent anticipation of "α5β1 antagonist" are lacking. For example,[39]

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[37] Neri *et al.* "Targeting by affinity-matured recombinant antibody fragments of an angiogenesis associated fibronectin isoform." Nat Biotechnol. 1997 Nov;15(12):1271-5.

[38] Mariani *et al.* "Tumor targeting potential of the monoclonal antibody BC-1 against oncofetal fibronectin in nude mice bearing human tumor implants. Cancer. 1997 Dec 15;80(12 Suppl):2378-84.

[39] Applicant also incorporates her additional prior arguments that (1) the Examiner conceded that Pasqualini *et al.* does **not** disclose an "agent that interferes with specific binding of the α5β1 integrin to a ligand," (2) the Examiner **admitted** that Pasqualini *et al.* "does not specifically state that the . . . ligand is fibronectin," (3) the Examiner **admitted** that Pasqualini *et al.* fails to disclose Claim 2's limitation that the "agent does not substantially interfere with the specific binding of a ligand to an integrin other than α5β1," (4) Applicant need **not** advance evidence demonstrating that the claimed method is functionally different than that taught by the prior art and to establish patentable differences because the Examiner has **not** met her burden of proving express anticipation, (5) the Examiner **admitted** that sFN's interference with the specific binding of α5β1 integrin to a ligand is only a **possible**, not a necessary, method by which sFN causes inhibition of angiogenesis, (6) the Examiner has not provided evidence that demonstrates that Pasqualini *et al.*'s inhibition of angiogenesis by administration of sFN is not caused by interference with the binding of **any one** of the α3β1, α4β1, αvβ1, α4β7, and αvβ3 receptors to their ligands, and is therefore **necessarily** caused by interference with the binding of α5β1 integrin to its ligand(s), (7) sFN has **opposite biological effects** compared to agents which are known to interfere with the specific binding of α5β1 integrin to its ligand(s) with respect to endothelial cell migration on collagen and also with respect to the comparative effect of endothelial cell migration on fibronectin versus collagen, and (8) the Examiner misapplies the legal test of inherency by continuing to improperly **speculate** on Pasqualini *et al.*'s disclosure.

Applicant argued that (1) Yi *et al.* demonstrates that the art continues to be **ignorant** of any mechanism for the antiangiogenic activity of sFN, much less that the mechanism "necessarily" involves the recited interference with binding to α5β1 integrin, (2) Yi *et al.* teaches that Pasqualini *et al.*'s sFN reduces metastasis by impacting **tumor** cells, not **endothelial** cells (which are involved in the recited angiogenesis), (3) Yi *et al.* suggests that, to the extent endothelial cells are involved, sFN acts via **αvβ3**, not **α5β1**, (4) Morla *et al.* teaches that the biological effects of Pasqualini *et al.*'s administration of sFN are not necessarily mediated via α5β1 integrin, but rather may be channeled through **other** receptors, (5) Varner *et al.* demonstrates the absence of α5β1 expression on Pasqualini *et al.*'s HT29 cells which is evidence that the effect of Pasqualini *et al.*'s sFN on HT29 cells **cannot possibly** (much less "necessarily") be mediated by sFN's interference with the binding of α5β1 integrin to a ligand.

The Examiner maintained her position regarding "the absence of objective evidence demonstrating that sFN does not act in the same manner as FN on the claimed receptor."[40] As discussed at the interview, however, the evidence was already presented in the references of record; when added to CAM in angiogenesis assays, whereas fibronectin **promotes** angiogenesis via α5β1,[41] sFN **inhibits** angiogenesis.[42] This further demonstrates that the antiangiogenic effect of Pasqualini's sFN is **not** mediated via α5β1 integrin.

As further discussed at the interview with respect to further distinguishing sFN from α5β1 antagonists, Applicant notes that new Claims 121-123 recite that the α5β1 antagonist "induces endothelial cell apoptosis." This is in contrast to Pasqualini *et al.* which does not disclose this limitation.[43] Also per the interview's discussion, Applicant provides an article by

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[40] Office Action, middle of page 8.

[41] Kim *et al.*; Specification, page 46, lines 20-32.

[42] Pasqualini *et al.*, Example X, columns 27-28.

[43] This amendment is not made in acquiescence to the Examiner's contention that further distinction of an "agent" over superfibronectin is necessary to impart novelty or non-obviousness. Rather, this amendment is made to expedite Applicant's business interests.

Pasqualini *et al.* (Tab 5)[44] that supports this further distinction by teaching that superfibronectin (sFN) "did not affect cell viability."[45]

Since Pasqualini *et al.* does not disclose all the limitations of the claims, Applicant respectfully requests that the rejection of Claims 1-5, 9-13, 55-66, 68, 69, 71, 72, 75, and 80-120 under 35 U.S.C. §102(e) be withdrawn.

6. Rejection Of Claims 1-3, 9-13, 55, 57-63, 65, 66, 71, 72, 75, 80-97, 100-106, 108-117, 119, And 120 Under 35 U.S.C. §102(e) Over Pasqualini *et al.*

Claims 1-3, 9-13, 55, 57-63, 65, 66, 71, 72, 75, 80-97, 100-106, 108-117, 119, and 120 stand rejected under 35 U.S.C. §102(e) as being allegedly anticipated by Pasqualini *et al.* (U.S. Patent No. 5,922,676) as evidenced by Ruoslahti *et al.* (WO 95/14714).[46] Applicant respectfully traverses.

As discussed at the interview, Ruoslahti *et al.* does not add to the above-discussed deficiency of Pasqualini *et al.* (item 5 of this communication) since neither Ruoslahti *et al.* nor Pasqualini *et al.* disclose that Pasqualini *et al.*'s sFN is an "$\alpha 5\beta 1$ antagonist" (recited in each pending claim) or "induces endothelial cell apoptosis" (recited in the new claims).

In addition, Applicant incorporates herein each of her prior arguments and evidence that were presented in the Responses mailed on 2/19/02 and 9/5/01 in support of the further deficiencies of Ruoslahti *et al.*

Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. §102(e) be withdrawn.

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[44] Pasqualini *et al.* (1996) "A polymeric form of fibronectin has antimetastatic effects against multiple tumor types," Nature Medicine 2(1):1197-1203.

[45] Pasqualini *et al.* (1996), page 1197, column 2, last paragraph.

[46] Office Action, page 11, item 9.

7. Rejection Of Claims 80-106, 108-117, 119, And 120 Under 35 U.S.C. §102(e) Over Pasqualini *et al.*

Claims 80-106, 108-117, 119, and 120 stand rejected under 35 U.S.C. §102(e) for alleged anticipation by Pasqualini *et al.* (U.S. Patent No. 5,922,676) as evidenced by Ruoslahti *et al.* (WO 95/14714) and Pytela *et al.*[47] Applicant respectfully disagrees.

Pytela *et al.*'s disclosure does not add to the deficient disclosures of either Pasqualini *et al.* or Ruoslahti *et al.* for the reasons discussed *supra* (items 5 and 6 of this communication), namely that none of the references discloses that Pasqualini *et al.*'s sFN is an "$\alpha 5\beta 1$ antagonist" or "induces endothelial cell apoptosis."

Furthermore, Pytela *et al.* relates to fibronectin, not to Pasqualini *et al.*'s sFN, thus anticipation by Pasqualini *et al.* is not established.

In addition, Applicant incorporates herein each of her prior arguments and evidence that were presented in the Responses mailed on 2/19/02 and 9/5/01 with respect to the deficiency of Pasqualini *et al.*, Ruoslahti *et al.*, and Pytela *et al.*

In view of the above, withdrawal of the rejection under 35 U.S.C. §102(e) is respectfully requested.

8. Rejection Of Claims 1-5, 9-13, 19, 20, 55-72, 75, 80-106, 108-117, 119, And 120 Under 35 U.S.C. §103(a) Over Pasqualini *et al.* In View Of Ruoslahti *et al.*, Thorpe, And Pytela *et al.*

Claims 1-5, 9-13, 19, 20, 55-72, 75, 80-106, 108-117, 119, and 120 stand rejected under 35 U.S.C. §103(a) for alleged obviousness over Pasqualini *et al.* (U.S. Patent No. 5,922,676) as evidenced by Ruoslahti *et al.* (WO 95/14714), Thorpe, and Pytela *et al.* Applicant respectfully traverses because a *prima facie* case of obviousness is not established. Furthermore, even if a *prima facie* case is arguably made, it is rebutted by Applicant's evidence.

A. A *prima facie* Case Of Obviousness Is Not Made

A *prima facie* case of obviousness requires the Examiner to cite to a combination of references which (a) suggests or motivates one of skill in the art to modify their teachings to

[47] Office Action, page 12, item 10.

yield the claimed invention, (b) discloses the elements of the claimed invention, **and** (c) provides a reasonable expectation of success should the claimed invention be carried out. Failure to establish **any** one of these requirements precludes a finding of a *prima facie* case of obviousness and, without more, entitles Applicant to withdrawal of the rejection of the claims in issue.[48] Applicant urges that **all three** requirements are absent, as discussed below.

1. The Combined References Fail To Disclose All The Limitations Of The Claims

It is axiomatic for establishing a *prima facie* case of obviousness that "all the claim limitations must be taught or suggested by the prior art."[49] However, none of Pasqualini *et al.*, Ruoslahti *et al.*, or Pytela *et al.* discloses that Pasqualini *et al.*'s sFN is an "$\alpha 5\beta 1$ antagonist" or "induces endothelial cell apoptosis" as discussed *supra* (items 5-7 of this communication). Thorpe does not bridge the gap in these references since Thorpe relates to arming antibodies with cytotoxic agents, not to $\alpha 5\beta 1$ antagonists or to inducing endothelial cell apoptosis.

Applicant also incorporates herein each of her prior arguments and evidence that were presented in the Responses mailed on 2/19/02 and 9/5/01.

Because this fundamental prong of a *prima facie* case of obviousness is lacking, a *prima facie* case of obviousness cannot be established.

2. The Combined References Do Not Provide A Motivation To Practice The Recited Combination Of Steps

An essential requirement for a *prima facie* case of obviousness is whether a person skilled in the art would be **motivated** to modify the reference to arrive at the **claimed invention**.[50] In particular,

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[48] See, *e.g.*, *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

[49] MPEP § 2143.03, citing *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

[50] *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988) and *In re Jones*, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992).

> "the examiner must show *reasons* that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the *claimed invention*, would select the elements from the cited prior art references for combination in the manner claimed."[51]

Applicant incorporates her prior arguments that (1) there is no motivation for "reducing or inhibiting angiogenesis" by using the recited "α5β1 antagonist that interferes with specific binding of the α5β1 integrin" because the prior art **did not know** that α5β1 integrin expression was associated with angiogenesis, and because the instant Specification is the **first** report of such an association, (2) the Examiner relies on impermissible **hindsight** because the art did not teach a nexus between α5β1 and reducing angiogenesis, (3) inherency has **no** place in an obviousness analysis and is **not a substitute** for some teaching or suggestion supporting an obviousness rejection, (4) Pasqualini *et al.*'s disclosure of **topical** administration of sFN is irrelevant to rejected Claims 1-5, 9-14, 19, 20, 55-72, and 75 because none of these claims recites (albeit the claims encompass) administration of the agent using **eye drops**, (5) Pasqualini *et al.*'s disclosure of **cytotoxin-linked agents** adds nothing to the reference's inadequate motivation for reducing or inhibiting **angiogenesis** by interfering with α5β1's binding to an integrin, (6) alleged motivation to inject the agents directly into Pasqualini *et al.*'s or Ruoslahti *et al.*'s tumors is irrelevant to Claims 1-5, 9-14, 19, 20, 55-66, 68-72, 75, 80-106, 108-117, 119, and 120 because none of these claims recites (albeit the claims encompass) **injecting** the agent,[52] and (7) an alleged motivation to **inject** an agent directly into a tumor fails to supplement the insufficient motivation for reducing or inhibiting **angiogenesis** by interfering with **α5β1**'s binding to an integrin, as explained above.

In view of the above, a motivation to combine the teachings of the references to arrive at the claimed invention is lacking. This alone negates a *prima facie* case of obviousness.

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[51] (Emphasis added) *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998); *Robotic Vision Systems Inc. v. View Engineering Inc.*, 51 USPQ2d 1948 (Fed. Cir. 1999).

[52] Applicant avers that these claims nonetheless encompass injecting the agent.

3. A Reasonable Expectation Of Success Is Not Established

A fundamental requisite of establishing a *prima facie* case of obviousness is that there be a reasonable expectation of success in practicing the recited method steps.

> "[T]he reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure."[53]

Applicant incorporates her prior arguments that (1) any alleged expectation of success is rebutted by the prior art's ignorance of a role for α5β1 integrin in angiogenesis, (2) obviousness cannot be predicated on what is unknown, and (3) even if inherency were improperly resorted to, inherency is lacking as discussed *supra*.

Because, not one, but each of the **three** elements of a *prima facie* case of obviousness is lacking, the rejection under 35 U.S.C. § 103(a) for alleged obviousness should be withdrawn.

B. Applicant's Evidence Rebuts Obviousness

Even assuming, *arguendo*, that a *prima facie* case of obviousness is made, Applicant incorporates herein her prior arguments and evidence which rebuts both the motivation to combine the references as well a reasonable expectation of success when practicing the combination.

Motivation to combine the teachings of Pasqualini *et al.* with any other reference is rebutted by (1) Yi *et al.* that **teaches away** from the claimed invention by proposing that sFN acts either by impacting tumor cells rather than endothelial cells, or by binding to αvβ3 integrin, not α5β1 integrin, (2) Morla *et al.* and Varner *et al.* that **teach away** from the claimed methods because they demonstrate that several receptors other than α5β1 mediate the function of sFN, (3) Ruoslahti *et al.* validates Varner *et al.*'s and Morla *et al.*'s **teaching away** from the claimed methods because it teaches that peptides which inhibit binding of α5β1 to a ligand function by inhibiting the **attachment** of **tumor cells** to fibronectin, rather than by the recited reduction of **angiogenesis** by **endothelial cells**, and (4) Pasqualini *et al.* and Kim *et al.* that **teach away** from considering Pasqualini *et al.*'s sFN as the recited "α5β1

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[53] *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) as cited in *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

antagonist" because they show that sFN is **functionally different** from α5β1 antagonists with respect to the effect on cell migration on fibronectin and collagen.

A reasonable expectation of success in inhibiting angiogenesis by using an α5β1 antagonist to interfere with the binding of α5β1 to a ligand is rebutted by (1) Yi *et al.*'s teaching that sFN impacts **tumor** cells rather than **endothelial** cells, and/or **αvβ3** rather than **α5β1**, (2) Morla *et al.* which shows that if the artisan arguably were to select α5β1, they would not have a reasonable basis for predicting that **this** particular receptor, from among the several **other possible** receptors, would be the one which mediates sFN's function in inhibiting angiogenesis, (3) Ruoslahti *et al.* from which the artisan would not reasonably expect that interference with a mechanism that is different from **tumor** cell **attachment** (*i.e.*, the recited reduction of **angiogenesis**) would account for sFN's effects, and (4) Pasqualini *et al.* and Kim *et al.* which demonstrate that sFN **functions differently** from α5β1 antagonists, and from which the artisan would **not** have a **reasonable basis for predicting** that sFN would have a **similar** effect (*i.e.*, reducing angiogenesis) as that caused by the recited "α5β1 antagonist."

Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 103(a) for alleged obviousness.

9. Rejection Of Claims 1-5, 9-14, 19, 20, 55-72, 75, And 80-120 Under 35 U.S.C. §103(a) Over Pasqualini *et al.* In View Of Ruoslahti *et al.*

Claims 1-5, 9-14, 19, 20, 55-72, 75, and 80-120 stand rejected under 35 U.S.C. §103(a) for alleged obviousness over Pasqualini *et al.* (U.S. Patent No. 5,922,676) as evidenced by Ruoslahti *et al.* (WO 95/14714).[54] Applicant cannot agree because a *prima facie* case of obviousness is absent and is rebutted by Applicant's evidence.

A. A prima facie Case Of Obviousness Is Absent

First, the combined references do not disclose all the limitations of the claims; neither Pasqualini *et al.* nor Ruoslahti *et al.* discloses that Pasqualini *et al.*'s sFN is an "α5β1 antagonist" or "induces endothelial cell apoptosis" as discussed *supra* (items 5-6 of this

[54] Office Action, page 17, item 12.

communication). Applicant also incorporates herein her prior arguments and evidence that were presented in the Responses mailed on 2/19/02 and 9/5/01. Because this prong of a *prima facie* case of obviousness is absent, a *prima facie* case of obviousness must fail.

Second, motivation is absent; Applicant incorporates herein her prior arguments and evidence that were presented in the Response mailed on 2/19/02 and 9/5/01 that (1) Ruoslahti *et al.* and Pasqualini *et al.* **did not know** that the peptides which they used caused a reduction or inhibition of angiogenesis by interfering with $\alpha 5\beta 1$ binding to a ligand, and (2) the Examiner is prohibited from using what is **unknown** to the art to establish motivation. Thus, this prong of a *prima facie* case of obviousness must fail, necessitating withdrawal of the rejection for alleged obviousness.

Third, a reasonable expectation of success remains unestablished; Applicant incorporates herein her prior arguments and evidence that were presented in the Responses mailed on 2/19/02 and 9/5/01 in that an alleged expectation of success is contradicted by the cited prior art's **ignorance** of a role for $\alpha 5\beta 1$ integrin in angiogenesis, let alone that the peptides of Pasqualini *et al.* or Ruoslahti *et al.* are "$\alpha 5\beta 1$ antagonists" which function by "reducing or inhibiting angiogenesis."[55] Thus, the third prong of a *prima facie* case of obviousness is absent.

Because a *prima facie* case of obviousness is unestablished, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 103(a) for alleged obviousness.

B. Applicant's Evidence Rebuts Obviousness

Applicant incorporates herein her prior arguments and evidence that were presented in the Responses mailed on 2/19/02 and 9/5/01, that even if a *prima facie* case of obviousness were arguably established (which it was not), it is rebutted by (1) Ruoslahti *et al.*'s teaching that peptides which inhibit binding $\alpha 5\beta 1$ to a ligand function by inhibiting the **attachment** of **tumor cells** to fibronectin, rather than by the recited reduction of **angiogenesis** by **endothelial cells**, (2) Ruoslahti *et al.* directs the skilled in the art to **expect** that its (and Pasqualini *et*

[55] Applicant also incorporates by reference its above argument that inherency cannot be used to establish obviousness.

al.'s) peptides function by inhibiting **cell attachment** by **tumor cells** and not by another mechanism, including the recited mechanism of reducing angiogenesis.

Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 103(a) for alleged obviousness.

CONCLUSION

All grounds of rejection and objection of the Office Action of May 21, 2002 having been addressed, reconsideration of the application is respectfully requested. As discussed at the August 5, 2002 interview, Applicant respectfully requests that the Examiner contact the undersigned collect at (415) 904-6500 or (510)237-8552 to discuss any outstanding issues **prior to beginning to draft another written communication**, if any.

Signed on behalf of:

Dated: November 21, 2002

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APPENDIX I

MARKED-UP VERSION OF REWRITTEN CLAIMS

Amend Claims 1, 2, 13, 19, 55, 57, 65-67, 70-72, 75, 80, 82, 84, 86, 90, 92, 94, 96, 106, 108, 110, 112, 114, 116, 117, and 119, and add the following Claims 121-123. Brackets denote deleted text, and underlining denotes inserted text.

1. (Once Amended) A method of reducing or inhibiting angiogenesis in a tissue, comprising contacting $\alpha5\beta1$ integrin in the tissue with an [agent] $\underline{\alpha5\beta1\ \text{antagonist}}$ that interferes with specific binding of the $\alpha5\beta1$ integrin to a ligand expressed in the tissue, thereby reducing or inhibiting angiogenesis in the tissue.

2. (Once Amended) The method of claim 1, wherein the [agent] antagonist does not substantially interfere with the specific binding of a ligand to an integrin other than $\alpha5\beta1$ integrin to its ligand.

13. (Once Amended) The method of claim 1, wherein the [agent] antagonist comprises a peptide.

19. (Once Amended) The method of claim 1, wherein the [agent] antagonist is linked to a cytotoxin.

55. (Once Amended) A method of reducing or inhibiting angiogenesis in a tissue in an individual, comprising administering to the individual an [agent] $\underline{\alpha5\beta1\ \text{antagonist}}$ that interferes with the specific binding of $\alpha5\beta1$ integrin to a ligand expressed in the tissue, thereby reducing or inhibiting angiogenesis in the tissue in the individual.

57. (Once Amended) A method of reducing the severity of a pathological condition associated with angiogenesis in an individual, comprising administering to the individual an [agent] $\underline{\alpha5\beta1\ \text{antagonist}}$ that interferes with specific binding of $\alpha5\beta1$ integrin to a ligand in a tissue associated with the pathological condition, thereby reducing or inhibiting angiogenesis in the tissue, and reducing the severity of the pathological condition.

65. (Once Amended) The method of claim 57, wherein the [agent] antagonist is administered intravenously.

66. (Once Amended) The method of claim 57, wherein the [agent] antagonist is administered orally.

67. (Once Amended) The method of claim 58, wherein the [agent] antagonist is administered into a neoplasm.

70. (Once Amended) The method of claim 68, wherein the [agent] antagonist is administered in the form of eye drops.

71. (Once Amended) The method of claim 68, wherein the [agent] antagonist is administered intravenously.

72. (Once Amended) The method of claim 68, wherein the [agent] antagonist is administered orally.

75. (Once Amended) The method of claim 57, wherein the [agent] antagonist is administered at a dose of 0.0001 to 100 mg/kg body weight.

80. (Once Amended) The method of Claim 1, wherein the binding of said [agent] antagonist to said $\alpha 5\beta 1$ integrin is at least two-fold greater than the binding of said [agent] antagonist to an integrin other than $\alpha 5\beta 1$ integrin.

82. (Once Amended) The method of Claim 1, wherein the binding of said [agent] antagonist to said $\alpha 5\beta 1$ integrin is at least five-fold greater than the binding of said [agent] antagonist to an integrin other than $\alpha 5\beta 1$ integrin.

84. (Once Amended) The method of Claim 1, wherein the binding of said [agent] antagonist to said $\alpha 5\beta 1$ integrin is at least ten-fold greater than the binding of said [agent] antagonist to an integrin other than $\alpha 5\beta 1$ integrin.

86. (Once Amended) The method of Claim 1, wherein said [agent] antagonist does not interfere with the specific binding of a ligand to an integrin other than $\alpha 5\beta 1$ integrin.

90. (Once Amended) The method of Claim 55, wherein the binding of said [agent] antagonist to said $\alpha 5\beta 1$ integrin is at least two-fold greater than the binding of said [agent] antagonist to an integrin other than $\alpha 5\beta 1$ integrin.

92. (Once Amended) The method of Claim 55, wherein the binding of said [agent] antagonist to said $\alpha 5\beta 1$ integrin is at least five-fold greater than the binding of said [agent] antagonist to an integrin other than $\alpha 5\beta 1$ integrin.

94. (Once Amended) The method of Claim 55, wherein the binding of said [agent] antagonist to said $\alpha 5\beta 1$ integrin is at least ten-fold greater than the binding of said [agent] antagonist to an integrin other than $\alpha 5\beta 1$ integrin.

96. (Once Amended) The method of Claim 55, wherein said [agent] antagonist does not interfere with the specific binding of a ligand to an integrin other than $\alpha 5\beta 1$ integrin.

106. (Once Amended) The method of Claim 55, wherein said [agent] antagonist comprises a peptide.

108. (Once Amended) The method of Claim 55, wherein said [agent] antagonist is linked to a cytotoxin.

110. (Once Amended) The method of Claim 57, wherein the binding of said [agent] antagonist to said α5β1 integrin is at least two-fold greater than the binding of said [agent] antagonist to an integrin other than α5β1 integrin.

112. (Once Amended) The method of Claim 57, wherein the binding of said [agent] antagonist to said α5β1 integrin is at least five-fold greater than the binding of said [agent] antagonist to an integrin other than α5β1 integrin.

114. (Once Amended) The method of Claim 57, wherein the binding of said [agent] antagonist to said α5β1 integrin is at least ten-fold greater than the binding of said [agent] antagonist to an integrin other than α5β1 integrin.

116. (Once Amended) The method of Claim 57, wherein said [agent] antagonist does not interfere with the specific binding of a ligand to an integrin other than α5β1 integrin.

117. (Once Amended) The method of Claim 57, wherein said [agent] antagonist comprises a peptide.

119. (Once Amended) The method of Claim 57, wherein said [agent] antagonist is linked to a cytotoxin.

121. (New) A method of reducing or inhibiting angiogenesis in a tissue, comprising contacting α5β1 integrin in the tissue with an α5β1 antagonist that induces endothelial cell apoptosis and interferes with specific binding of the α5β1 integrin to a ligand expressed in the tissue, thereby reducing or inhibiting angiogenesis in the tissue.

122. (New) A method of reducing or inhibiting angiogenesis in a tissue in an individual, comprising administering to the individual an α5β1 antagonist that induces endothelial cell apoptosis and interferes with the specific binding of α5β1 integrin to a ligand expressed in the tissue, thereby reducing or inhibiting angiogenesis in the tissue in the individual.

123. (New) A method of reducing the severity of a pathological condition associated with angiogenesis in an individual, comprising administering to the individual an α5β1 antagonist that induces endothelial cell apoptosis and interferes with specific binding of α5β1 integrin to a ligand in a tissue associated with the pathological condition, thereby reducing or inhibiting angiogenesis in the tissue, and reducing the severity of the pathological condition.